PATENT SPECIFICATION (11) 1 603 030

1 603 030

(21) Application No. 15863/78 (22) Filed 21 April 1978
(31) Convention Application No. 789723
(32) Filed 21 April 1977 in
(33) United States of America (US)
(44) Complete Specification published 18 Nov. 1981
(51) INT CL³ C07D 401/02 A61K 31/445 (C07D 401/02 209/04 211/06)
(52) Index at acceptance
C2C 1173 1343 1532 200 211 213 215 220 225 226 22Y 246 247 250 251 25Y 28X 29X 29Y 305 30Y 311 313 31Y 321 326 32Y 332 337 338 351 355 35X 35Y 364 365 36Y 386 401 407 40Y 453 45Y 485 620 621 623 624 625 62Y 660 661 662 665 672 675 676 681 68Y 694 697 698 699 69Y 708 73Y 74Y 77X 77Y 802 80Y AA AB MM NJ NR UJ UL WD ZB

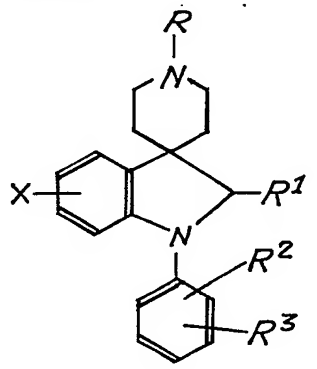
(19)

(54) SPIRO[INDOLINE-3,4'-PIPERIDINE]S AND RELATED COMPOUNDS

(71) We, HOECHST AKTIENGESELLSCHAFT, a Body Corporate organised according to the laws of the Federal Republic of Germany, of 6230 Frankfurt (Main) 80, Postfach 80 03 20, Federal Republic of Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

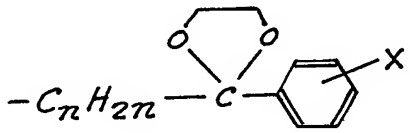
The present invention provides spiro[indoline - 3,4' - piperidine]s and related compounds of the general formula:

(I)



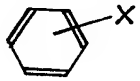
in which

R represents hydrogen or an alkyl, cyano, alkanoyl, phenylalkyl, phenylalkanoyl, alkenyl, cycloalkylalkyl, benzoyl or a benzoylalkyl radical or an ethylene glycol ketal radical of the formula



in which n is an integer of from 1 to 4;

R^1 represents hydrogen or an alkyl radical, a phenyl radical of the formula



or a biphenyl radical;

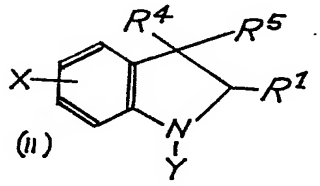
R^2 and R^3 are the same or different and each represent hydrogen or halogen or a trifluoromethyl, alkyl, alkoxy, hydroxy, nitro, amino or acylamino group; and

X represents hydrogen or halogen or an alkyl, alkoxy, hydroxy or trifluoromethyl group; and
in which in every case the alkyl radical or the alkyl moiety in the alkoxy, alkanoyl and alkenyl radicals is a lower alkyl radical containing up to 4 carbon atoms.

Physiologically tolerable salts of these compounds are included within the scope of the present invention. The term "lower" qualifying a radical in the above definitions means a radical containing up to 4 carbon atoms, and "cycloalkyl" means a saturated homocyclic ring of preferably 3 to 8 carbon atoms.

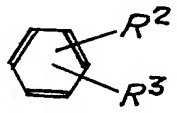
The compounds of this invention are new and find application as anti-depressants, anticonvulsants and tranquillisers.

The present invention also provides a process for the manufacture of a compound of the general formula

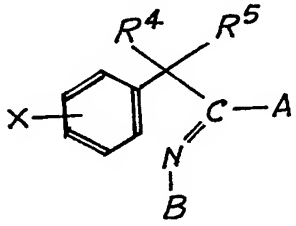


(II)

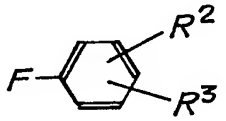
in which
Y represents hydrogen or



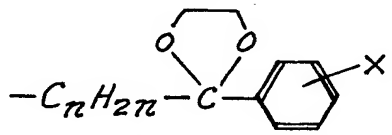
R^4 and R^5 each represent an alkyl, aminoalkyl, alkylaminoalkyl or a dialkylaminoalkyl radical,
in which in every case the alkyl moiety contains up to 4 carbon atoms, or R^4 and R^5 together with the carbon atom to which they are attached form a cycloalkyl moiety of 3 to 6 carbon atoms in which cycloalkyl a carbon atom may be replaced by >N—R, and
R^1, R^2, R^3, R and X have the meanings as defined above, which comprises reductively cyclizing a compound of the formula



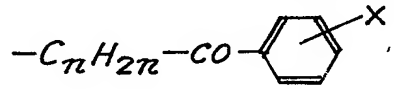
wherein A represents R^1, B represents hydrogen, or A and B together form an additional bond, R^4, R^5, X and R^1 are as defined above to provide a compound of the formula (II) wherein Y represents hydrogen and R^1, R^4, R^5 and X are as defined above, and reacting that compound with a compound of the formula



wherein R^2 and R^3 are as defined above, except that they cannot be hydroxy, amino or acylamino, to provide a compound of formula (II), wherein Y is not hydrogen, and, if desired, treating a compound of the formula (II), wherein R represents methyl, with cyanogen bromide to provide a compound of the general formula (I), wherein R represents cyano, and optionally splitting the cyano group to provide a compound of the formula (I), wherein R represents hydrogen and, if desired, alkylating or acylating that compound to provide a compound of the formula (I), wherein R is as defined above except that it is not hydrogen or cyano, and, if desired, hydrolyzing a compound of the formula (II), wherein R represents

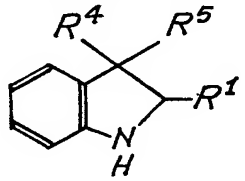


to provide a compound of the formula (II), wherein R represents



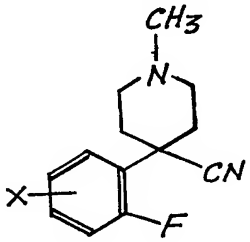
and, if desired, reducing a compound of the formula (II), wherein R contains a carbonyl group, to provide a compound of the formula (II), wherein the carbonyl group in R is replaced by a methylene group and, if desired, dealkylating a compound of the formula (II), wherein X, R^2 and/or R^3 each represent an alkoxy group, to provide the corresponding phenolic compound, and, if desired, reducing a compound of the formula (II), wherein R^2 or R^3 represents nitro, to provide the corresponding amino compound and, if desired, acylating a compound of the formula (I), wherein R^2 and/or R^3 represent amino to provide the corresponding acylamino compound.

The process of the present invention involves cyclizing a molecule which contains the groups R^4 and R^5 as hereinbefore defined, especially a piperidino moiety. It gives very good yields. The closure of an isoindole ring by formation of a C—N bond is not specific to the indolines of this invention but is generic with respect to all 3,3-di-substituted indolines. The invention thus also includes a new and preferred vehicle for producing indoline rings which are depicted as follows:

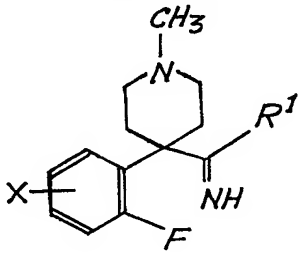


in which R^1, R^4 and R^5 have the meanings given above. In this regard, the invention is not limited by substituents which may be present on said indoline ring.

A precursor of the compounds of the invention, a 4 - cyano - 4 - (2 - fluorophenyl) - 1 - methylpiperidine of the formula:



wherein X represents hydrogen or halogen or a lower alkoxy, CF_3 or nitro group, is prepared by the reaction of a 2 - fluorophenylacetonitrile and mechloroethamine hydrochloride. The reaction may be carried out in the presence of sodium hydride and a solvent such, for example, as dimethylformamide. Another precursor, a 4 - imino - 4 - (2 - fluorophenyl) - 1 - methylpiperidine of the formula:

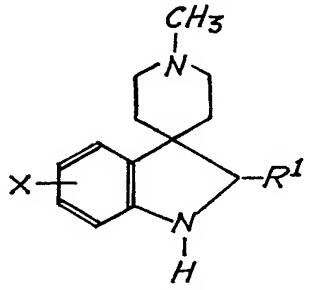


wherein R' represents alkyl or phenyl, may be prepared by treating 4 - cyano - 4 - (2 - fluorophenyl) - 1 - methylpiperidine of the above formula with phenyl- or alkyl-magnesium bromide in an ether solvent under the conditions of the Grignard reaction. The resulting compound is not fully hydrolyzed but treated with an aqueous saturated ammonium chloride solution leaving the imino compound as stable compound.

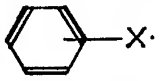
Any of the compounds of the invention can be prepared by one of the methods described below.

Method A

A 4-cyano or 4 - imino - 4 - (2 - fluorophenyl) - 1 - methylpiperidine of the formula given above is reductively cyclized to its corresponding 1' - methylspiro[indoline - 3,4' - piperidine], of the formula

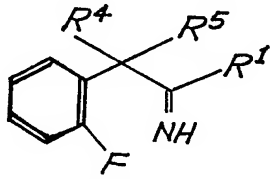


wherein R^1 represents hydrogen, a phenyl radical of the formula

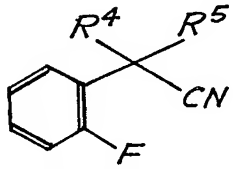


in which X has the meaning given above, biphenyl or lower alkyl. The cyclizing is carried out, for example, by utilizing lithium aluminium hydride as a cyclizing/reducing agent in a solvent such as 1,2-dimethoxyethane or tetrahydrofuran at a temperature of from ambient to reflux of the particular reaction mixture.

This procedure can be utilized to reduce and cyclize a compound depicted by the formula



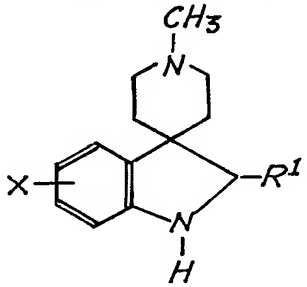
or



to provide a corresponding indoline ring structure, R^4 and R^5 being the same or different and each representing alkyl or aminoalkyl or, when taken together, forming a cyclic moiety.

Method B

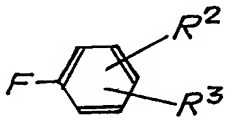
A 4 - cyano - 4 - (2 - fluorophenyl) - 1 - methylpiperidine of the formula given above is treated according to the conditions of the Grignard reaction with a Grignard reagent of the formula R'Mg—Y wherein R' is alkyl or phenyl and Y is bromine or chlorine to produce the corresponding cyclic compound (3-H-indole) which is in turn reduced to produce a 2-alkyl, phenyl or biphenyl substituted 1' - methylspiro[indoline - 3,4' - piperidine], of the formula



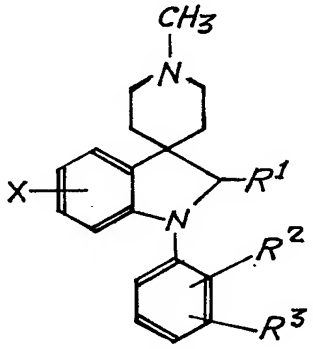
The above reaction can be carried out with sodium borohydride or lithium aluminium hydride as the reducing agent and ethanol or tetrahydrofuran, respectively, as the solvent.

Method C

A compound prepared by method A or B can be treated with a fluorophenyl compound of the formula



wherein R^2 and R^3 are as defined earlier except they cannot be hydroxy, amino or acylamino, in a solvent such as dimethylformamide or dimethylsulphoxide and in the presence of a reaction initiator such, for example, as sodium hydride at a temperature of from ambient to the boiling point of the solvent to provide a 1 - phenyl - 1' - methylspiro[indoline - 3,4' - piperidine], a compound of the invention of the formula



Method D

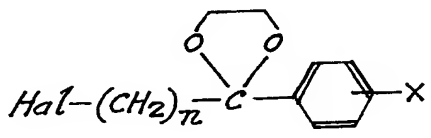
A compound of the invention wherein R is methyl prepared according to Method A, B or C can be treated with cyanogen bromide in a solvent such, for example, as dichloromethane with an agent neutralising acids such, for example, as potassium carbonate, at ambient temperature to produce the corresponding compound of the invention wherein R is cyano.

Method E

A cyano compound prepared by Method D can be treated with hydrochloric acid in an aqueous solution to split the cyano group, yielding a compound of the invention in which R is H.

Method F

A compound prepared by Method E can be alkylated or acylated, for example, by reaction in a known manner with an alkanoyl-halide or -anhydride, benzoyl-halide or -anhydride, benzyl halide, phenylalkanoyl halide, alkyl halide, alkenyl halide, cycloalkylcarbonyl halide or benzoylalkyl halide, to produce the corresponding spiro[indoline - 3,4' - piperidine]substituted in the 1'-position by an alkanoyl, benzoyl, phenylalkanoyl, alkyl, alkenyl, cycloalkylcarbonyl, phenylalkyl or benzylalkyl radical. Alternatively, a compound of the invention in which R is an ethylene glycol ketal produced by reacting a compound in which R is hydrogen with a compound of the formula



in which n is 1 to 4 can be hydrolyzed.

Method G

A 1'-acyl compound prepared by Method F can be reduced by a convenient method known *per se* to produce the corresponding 1'-alkyl, cycloalkyl-alkyl or phenyl-alkyl compound, a compound of the invention. One such suitable method involves the use of lithium aluminium hydride as the reducing reagent.

Method H

A compound of the invention in which X, R^2 or R^3 is an alkoxy group prepared by any of the above methods and can be dealkylated by a method known *per se* to produce the corresponding phenolic (X, R^2 and/or R^3=OH) compounds of the invention. One such method involves treatment with 48% hydrobromic acid.

Method I

A compound of the invention in which R^2 or R^3 is nitro can be reduced by a known method to give the corresponding compound of the invention in which R^2 or R^3 is amino. One such method is catalytically reducing with a palladium on carbon catalyst.

Method J

A compound prepared in Method I can be acylated by a known method to give the corresponding compound in which R^2 or R^3 is acylamino, preferably acetamido. One such acylation is carried out with acetic anhydride.

Acids useful for preparing the pharmaceutically acceptable acid addition salts of the invention include mineral acids such, for example, as hydrochloric, hydrobromic, sulphuric, nitric, phosphoric and perchloric acids, as well as organic acids such, for example, as tartaric, citric, acetic, succinic, maleic, fumaric and oxalic acids.

The compounds of the present invention are useful in the treatment of depression in mammals, as demonstrated by their ability to enhance the central noradrenergic and/or serotonergic nervous function. This ability was measured in rats according to the 5' - L - hydroxytryptophan Potentiation Procedure [H. Sigg, E.B., Psychiatr. Assoc. J., 4 (Suppl.); 75—85 (1959)]. In this procedure, groups of six male Wistar rats were utilized. Four hours prior to testing freshly prepared pargyline hydrochloride is subcutaneously administered. Thirty minutes before testing, drugs are intraperitoneally administered. Finally L-5-hydroxytryptophan is administered intraperitoneally and five minutes after administration the rats are observed for fifteen minutes. A compound is considered to potentiate 5-L-hydroxytryptophan activity if the rats exhibit head motion (twitching) accompanying coarse tremors. Using this test an ED50, dose effecting a 50% potentiation, is ascertained for any particular compound. For example, 1' - methyl - 1 - [(4 - trifluoromethyl) - phenyl]spiro[indoline - 3,4' - piperidine] shows an ED50 of 7.8 mg/kg. i.p. This datum illustrates that compounds of the invention are useful as antidepressants for mammals when administered in amounts ranging from about 0.1 to 50 mg/kg body weight per day.

The usefulness of the compounds of the present invention in the treatment of depression in mammals is further demonstrated by their ability to inhibit tetrabenazine-induced ptosis in mice [International Journal of Neuropharmacology, 8, 73 (1969)] a standard assay useful for evaluating antidepresant properties. Thus, for instance, 1 - (2 - chlorophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine]maleate and 1 - (2 - fluorophenyl) - 1' - methylspiro - [indoline - 3,4' - piperidine]maleate each effect a 50% inhibition from the ptosis of tetrabenazine-induced depression in mice at the dose of 3.2 and 4.0 mg/kg, p.o., respectively.

Compounds of the present invention are further useful as anticonvulsant agents for mammals, as determined by the method of Woodbury, L.A. and Davenport, V.D. in Arch., Int. Pharmacodynam, Vol. 92 (1952) at pp 97—107. For example, the intraperitoneal dose of 17.3 mg/kg of body weight of 1' - methyl - 1 - [(4 - trifluoromethyl) - phenyl]spiro[indoline - 3,4' - piperidine] produces a 50% protection from the effect of supramaximal electro shock (SES). Similar effects are produced by the intraperitoneal doses of 10.6, 18.5, 19.2 and 38.4 mg/kg of 1 - (2 - fluorophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine]maleate, 1 - (4 - fluorophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine]hydrobromide, 1 - (4 - chlorophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine] and 1 - (2 - chlorophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine]maleate, respectively. This data illustrates that compounds of the invention are useful in treating

convulsions in mammals when administered in amounts ranging from about 0.1 to 50 mg/kg of body weight per day.

Compounds of the present invention are further useful as tranquillizers due to their ability to depress the central nervous system of mammals.

Compounds of this invention include:

1' - ethyl - 1 - (3,4 - dimethylphenyl)spiro[indoline - 3,4' - piperidine];
1' - methyl - 6 - methoxy - 1 - phenylspiro[indoline - 3,4' - piperidine];
5 - fluoro - 1 - (4 - chlorophenyl) - 1' - phenylethylspiro[indoline - 3,4' - piperidine];
1 - (4 - methoxyphenyl)spiro[indoline - 3,4' - piperidine];
1 - (4 - hydroxyphenyl)spiro[indoline - 3,4' - piperidine];
1' - phenethyl - 1 - phenylspiro[indoline - 3,4' - piperidine];
1' - methyl - 1,2 - diphenylspiro[indoline - 3,4' - piperidine];
1' - cyclopropylmethyl - 1 - (3 - methoxyphenyl)spiro[indoline - 3,4' - piperidine];
1' - allyl - 1 - (3 - hydroxyphenyl)spiro[indoline - 3,4' - piperidine];
1' - methyl - 2 - (4 - methylphenyl) - 1 - phenylspiro[indoline - 3,4' - piperidine]; and
1' - methyl - 5 - hydroxy - 1 - phenylspiro[indoline - 3,4' - piperidine].

Effective quantities of the compounds of the invention may be administered to a patient by any one of various methods, for example, orally as in capsules or tablets, parenterally in the form of sterile solutions or suspension, and in some cases intravenously in the form of sterile solutions. The free base final products, while effective themselves, may be formulated and administered in the form of their pharmaceutically acceptable addition salts for purposes of stability, convenience of crystallization and increased solubility.

The present invention accordingly also provides a pharmaceutical preparation which comprises a compound of the general formula (I) given above or a physiologically tolerable salt thereof in admixture or conjunction with a pharmaceutically suitable carrier.

The active compounds of the present invention may be orally administered, for example, with an inert diluent or with an edible carrier, or they may be enclosed in gelatin capsules, or they may be compressed into tablets. For the purpose of oral therapeutic administration, the active compounds of the invention may be incorporated with excipients and used in the form of tablets, troches, capsules, elixirs, suspensions, syrups, wafers, chewing gum and the like. These preparations should contain at least 0.5% of active compound, but may be varied depending upon the particular form and may conveniently be between 4% to about 70% of the weight of the unit. The amount of active compound in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present invention are prepared so that an oral dosage unit form contains between 1.0—300 milligrams of active compound.

The tablets, pills, capsules and troches may also contain the following ingredients: a binder such, for example, as microcrystalline cellulose, gum tragacanth or gelatin; an excipient such, for example, as starch or lactose, a disintegrating agent such, for example, as alginic acid, and corn starch; a lubricant such, for example, as magnesium stearate; a glidant such, for example, as colloidal silicon dioxide; and a sweetening agent such, for example, as sucrose or saccharin may be added or a flavouring agent such, for example, as peppermint, methyl salicylate, or orange flavouring. When the dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil. Other dosage unit forms may contain other various materials which modify the physical form of the dosage unit, for example, as coatings. Thus, tablets or pills may be coated with sugar, shellac, or other enteric coating agents. A syrup may contain, in addition to the active compounds, sucrose as a sweetening agent, and certain preservatives, dyes and colourings and flavours. Materials used in preparing these various compositions should be pharmaceutically pure and non-toxic in the amounts used.

For the purpose of parenteral therapeutic administration, the active compounds of the invention may be incorporated into a solution or suspension. These preparations should contain at least 0.1% of active compound, but may be varied to be between 0.5 and about 50% of the weight thereof. The amount of active compounds in such compositions is such that a suitable dosage will be obtained. Preferred compositions and preparations according to the present

invention are prepared so that a parenteral dosage unit contains between 0.5 to 100 milligrams of active compound.

The solutions or suspensions may also include the following components: a sterile diluent such, for example, as water for injection, saline solution, fixed oils, polyethylene glycols, glycerine, propylene glycol or other synthetic solvents; antibacterial agents such, for example, as benzyl alcohol or methyl parabens; antioxidants such, for example, as ascorbic acid or sodium bisulphite; chelating agents such, for example, as ethylene diaminetetraacetic acid; buffers such, for example, as acetates, citrates or phosphates, and agents for the adjustment of tonicity such, for example, as sodium chloride or dextrose. The parenteral preparation can be enclosed in ampoules, disposable syringes or multiple dose vials made of glass or plastic.

The invention further provides a method of treating a non-human mammal which comprises administering a compound of the general formula (I) given above.

The following Examples illustrate the invention:

Example 1

a). A solution of 14.9 g of 2-fluorophenylacetonitrile in 250 ml of dimethylformamide is added with vigorous stirring over a 5 minute span to 9.6 g of 99% sodium hydride. After total addition the reaction mixture is allowed to stand for 30 minutes at ambient temperature before a solution of 19.3 g of mechloroethamine hydrochloride in dimethylformamide is added dropwise. After total addition the reaction mixture is stirred at 90—95°C for 16 hours, leaving a very dark suspension. The suspension is poured onto ice water and the organic phase is extracted four times with 50 ml portions of ether. The combined extracts are shaken with an excess of 2 N HCl and the acidic extract is collected. The acidic solution is basified with cold ammonia leaving an oily amine which crystallizes with chilling. The solid is collected and recrystallized from hexane to give off-white crystals, mp 69—71°C, of 4 - cyano - 4 - (2 - fluorophenyl) - 1 - methylpiperidine. Infrared and nuclear magnetic resonance spectra confirm this structure.

b). A solution of 3.3 g of 4 - cyano - 4 - (2 - fluorophenyl) - 1 - methylpiperidine in 20 ml of 1,2-dimethoxyethane is added dropwise to a refluxing slurry of 800 mg of lithium aluminium hydride in 1,2-dimethoxyethane. After total addition the mixture is stirred at reflux for 64 hours and decomposed with successive portions of water, dilute sodium hydroxide and water. The granular aluminium oxide produced is filtered off and the filtrate is extracted three times with hot chloroform. The combined organic solution is washed with water and dried. The solvent is removed in vacuo leaving a thick oil which crystallizes on standing. The product is recrystallized from a benzene-hexane mixture to give prisms, mp 135—137°C, of 1′ - methylspiro[indoline - 3,4′ - piperidine].

c). A mixture of 0.9 g of 1′ - methylspiro[indoline - 3,4′ - piperidine], 2 g of 4-fluorobenzotrifluoride and 0.25 g of 50% sodium hydride in 20 ml of dimethylformamide is stirred under nitrogen at a temperature of 95°C for two hours. The mixture is allowed to cool, diluted with water and then extracted three times with 100 ml portions of ether. The combined ether extracts are back extracted with an excess of 2 N hydrochloric acid. The acidic solution is basified with potassium carbonate to give a product which is eluted with a 25% methanol in benzene mixture through a silica gel column to produce a pale yellowish oil which crystallizes with cooling. Recrystallization of these crystals from hexane gives rhombic crystals, mp 122—124°C, of 1′ - methyl - 1 - (4 - trifluoromethylphenyl)spiro[indoline - 3,4′ - piperidine].

Analysis:

Calculated for $C_{20}H_{21}F_3N_2$:	69.34% C;	6.11% H;	8.08% N;	16.45% F.
Found:	69.60% C;	6.25% H;	7.97% N;	16.25% F.

Example 2

By following the procedures of Example 1, but substituting 4-chlorofluorobenzene for 4-fluorobenzotrifluoride, produces pale yellowish crystals which are recrystallized from an ether-hexane mixture to give the product, mp 123—125°C, of 1 - (4 - chlorophenyl) - 1′ - methylspiro[indoline - 3,4′ - piperidine].

Analysis:

Calculated for $C_{19}H_{21}ClN_2$:	72.95% C;	6.77% H;	8.96% N;	11.33% Cl.
Found:	73.05% C;	6.70% H;	9.16% N;	11.36% Cl.

Example 3

A mixture of 0.95 g of 1 - (4 - chlorophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine] (Example 2), 0.42 g of cyanogen bromide and 1 g of potassium carbonate in 25 ml of dichloromethane is stirred at ambient temperature for two hours. The reaction mixture is filtered and the filtrate concentrated to dryness leaving an oily residue which is crystallized from an acetone-hexane mixture leaving colourless crystals, mp 178.5—180°C, of 1 - (4 - chlorophenyl) - 1' - cyanospiro[indoline - 3,4' - piperidine].

Analysis:

Calculated for $C_{19}H_{18}ClN_3$:	70.47% C;	5.60% H;	12.98% N.
Found:	70.30% C;	5.68% H;	13.03% N.

Example 4

A mixture of 1.6 g of 1' - methylspiro[indoline - 3,4' - piperidine] (Example 1b), 2.0 g of 50% sodium hydride and 3 ml of 3-fluorobenzotrifluoride in 15 ml of dimethyl sulphoxide is stirred at ambient temperature for one hour and then poured onto ice. The biphasic mixture is extracted three times with 100 ml portions of ether. The ether extracts are combined and dried and treated with hydrogen chloride to produce the salt. The solvent is decanted off, leaving a gummy salt which is basified with dilute ammonium hydroxide. The solvent is removed under reduced pressure, leaving a yellowish oil which solidifies on standing. The solid is recrystallized from pentane, leaving yellow coloured needles, mp 123—124.5°C, of 1 - (3 - trifluoromethylphenyl) - 1' - methylspiro[indoline - 3,4' - piperidine].

Analysis:

Calculated for $C_{20}H_{21}F_3N_2$:	69.34% C;	6.11% H;	8.08% N;	16.45% F.
Found:	69.52% C;	6.18% H;	8.00% N;	16.26% F.

Example 5

A mixture of 5.8 g of 1' - methylspiro[indoline - 3,4' - piperidine] (Example 1b), 5.0 g of 50% sodium hydride and 12 ml of 1,4-difluorobenzene in 50 ml of dimethylsulphoxide is stirred at 55—60°C for one hour. The mixture is allowed to cool and then diluted with water and extracted three times with 100 ml portions of ether. The ether extracts are extracted with an excess of 3 N hydrochloric acid and the acidic solution is basified leaving an oil which is dissolved in ether and dried. The ether is removed under reduced pressure, leaving a yellowish oil. The oil is eluted with a 10% methanolic methylene chloride mixture through a silica gel column packed in methylene chloride and then converted to a crystalline hydrobromide. The salt is recrystallized from a methanol-acetone-ether mixture, producing off-white granules, mp 267—269°C, of 1 - (4 - fluorophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine] hydrobromide.

Analysis:

Calculated for $C_{19}H_{21}FN_2 \cdot HBr$:	60.48% C;	5.96% H;	7.43% N.
Found:	60.32% C;	5.88% H;	7.28% N.

Example 6

A solution of 0.42 g of 1 - (4 - fluorophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine], the free base of Example 5, in 2 ml of chloroform is added dropwise to a refluxing mixture of 0.2 of cyanogen bromide and 0.4 g of potassium carbonate in 8 ml of chloroform. After total addition, the reaction mixture is stirred at ambient temperature for 16 hours and then filtered. The solvent is removed under reduced pressure, leaving a viscous oil which crystallizes on standing. These crystals are recrystallized from an acetone-hexane mixture to give off-white prisms, mp 139—140°C, of 1' - cyano - 1 - (4 - fluorophenyl)spiro[indoline - 3,4' - piperidine].

Analysis:

Calculated for $C_{19}H_{18}FN_3$:	74.23% C;	5.90% H;	13.67% N.
Found:	74.30% C;	5.93% H;	13.70% N.

Example 7

A mixture of 2.1 g of 1' - methylspiro[indoline - 3,4' - piperidine] (Example 1b), 3 g of 50% sodium hydride and 12 ml of fluorobenzene in 18 ml of dimethyl sulphoxide is stirred at 65—70°C for 45 hours. The well stirred mixture is poured into water and extracted three times with ether. The combined ether extracts are dried briefly before forming the hydrochloride salt. The salt is collected, basified and then extracted into ether, giving a yellowish oil which is crystallized from hexane, producing off-white crystals, mp 90—92°C of 1' - methyl - 1 - phenylspiro[indoline - 3,4' - piperidine].

Analysis:

Calculated for $C_{19}H_{22}N_2$:	81.96% C;	7.97% H;	10.06% N.
Found:	82.07% C;	8.09% H;	9.98% N.

Example 8

A mixture of 0.5 g of 1' - methyl - 1 - phenylspiro[indoline - 3,4' - piperidine] (Example 7), 0.5 g of potassium carbonate and 0.2 g of cyanogen bromide in 10 ml of methylene chloride is stirred at ambient temperature for two hours. The stirred mixture is filtered and the filtrate evaporated to dryness under reduced pressure. Eluting the residue with chloroform through a silica gel column packed in chloroform provides colourless crystals which are recrystallized from an acetone-hexane mixture to give fine granules, mp 136—138°C, of 1' - cyano - 1 - phenylspiro[indoline - 3,4' - piperidine].

Analysis:

Calculated for $C_{19}H_{19}N_3$:	78.85% C;	6.62% H;	14.52% N.
Found:	78.66% C;	6.53% H;	14.30% N.

Example 9

a). A solution of 4.4 g of 4 - cyano - 4 - (2 - fluorophenyl) - 1 - methylpiperidine (Example 1a), in 25 ml of tetrahydrofuran is added dropwise to a solution of 28 ml of phenylmagnesium chloride in tetrahydrofuran. After total addition the reaction mixture is stirred at reflux for 48 hours and decomposed with an excess of aqueous saturated ammonium chloride. The organic phase is extracted with ether and dried and the ether removed under reduced pressure, leaving a viscous oil which is applied on an alumina column packed in ether. Elution with ether removes a principal component which crystallizes on cooling to give colourless prisms, mp 168—169°C, of 1' - methyl - 2 - [(1,1' - biphenyl) - 2 - yl]spiro[3H - indole - 3,4' - piperidine]. Infrared, nuclear magnetic resonance and mass spectra confirm the assigned structure.

b). A solution of 250 mg of 1' - methyl - 2 - [(1,1' - biphenyl) - 2 - yl]spiro[3H - indole - 3,4' - piperidine] in 10 ml of tetrahydrofuran is added dropwise to a refluxing slurry of 100 mg of lithium aluminum hydride in 10 ml of tetrahydrofuran. After total addition, the reaction mixture is refluxed for three hours and then the mixture is decomposed with water, providing a crude oil. The oil is treated with ethereal-hydrobromide, producing a hydrobromide which is recrystallized from an ethanol-ether mixture to give off-white crystals, mp 267—270°C, (dec), of 2 - [(1,1' - biphenyl) - 2 - yl] - 1' - methylspiro[indoline - 3,4' - piperidine] dihydrobromide.

c). By following the procedure of Example 1c, 2 - [(1,1' - biphenyl) - 2 - yl] - 1' - methylspiro[indoline - 3,4' - piperidine], the free base of part b, is treated with 4-fluorobenzotrifluoride to provide 2 - [(1,1' - biphenyl) - 2 - yl] - 1' - methyl - 1 - (4 - trifluoromethyl)phenylspiro[indoline - 3,4' - piperidine].

Example 10

a). A solution of 4.4 g of 4 - cyano - 4 - (2 - fluorophenyl) - 1 - methylpiperidine (Example 1a), in 30 ml of sieve-dried 1,2-dimethoxyethane is added dropwise to a solution of 3M ethylmagnesium bromide in ether. After total addition the reaction mixture is stirred at a temperature of 80°C for 16 hours. The mixture is then decomposed with an excess of a saturated aqueous ammonium chloride solution and the organic phase is extracted with ether. The combined ether extracts are dried and the solvent is removed, leaving a crude residue. The residue is purified by eluting from an alumina column with ether, leaving a yellowish oil which is treated with a solution of 0.75 g of sodium borohydride in 15 ml of ethanol for 16 hours. The resulting product is converted, in ether, to its

dihydrobromide salt, which is recrystallized from methanol to give yellowish prisms, mp 250°C, of 2 - ethyl - 1' - methylspiro[indoline - 3,4' - piperidine] dihydrobromide.

b). By following the procedure of Example 1c, 2 - ethyl - 1' - methylspiro[indoline - 3,4' - piperidine], the free base of part a, is treated with 4-chlorofluorobenzene to yield 1 - (4 - chlorophenyl) - 2 - ethyl - 1' - methylspiro[indoline - 3,4' - piperidine].

Example 11

A reaction mixture of 2.6 g of 1' - methylspiro[indoline - 3,4' - piperidine] (Example 1b), 0.32 g of 98% sodium hydride and 2.8 ml of o-difluorobenzene in 20 ml of dimethyl sulphoxide is stirred at 55°C for ten minutes and then poured into a solution of 0.33 g of 98% sodium hydride with the reaction maintained at 55°C for an additional 60 minutes. The reaction mixture is then poured into 300 ml of ice-water and the biphasic mixture extracted three times with 100 ml portions of ether. The combined ether extracts are successively washed twice with 100 ml portions of water and extracted twice with 60 ml portions of 3 N hydrochloride acid. The acidic solution is basified to a pH of 10 with ammonia. The alkaline mixture is extracted twice with 100 ml portions of ether. The combined ether extracts are washed successively with a 100 ml portion of water and a 30 ml portion of a saturated sodium chloride solution and dried, leaving an oil. The oil is eluted through a silica gel column with a 5% methanol-dichloromethane mixture and then is dissolved in ether, where it is converted to its maleic acid salt. The salt is recrystallized from an acetone-ether mixture to give a white crystalline material, mp 209—210°C, of 1 - (2 - fluorophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine] maleate.

Analysis:

Calculated for $C_{19}H_{21}FN_2 \cdot C_4H_4O_4$:	66.97% C;	6.11% H;	6.79% N;	4.61% F.
Found:	66.70% C;	6.19% H;	6.87% N;	4.40% F.

Example 12

A mixture of 1' - cyano - 1 - phenylspiro[indoline - 3,4' - piperidine] (Example 8), is treated with 3 N hydrochloric acid to provide 1 - phenylspiro[indoline - 3,4' - piperidine].

Example 13

A mixture of 1 - phenylspiro[indoline - 3,4' - piperidine] (Example 12), propionyl chloride and sodium bicarbonate in chloroform is stirred at reflux. The mixture is allowed to cool, filtered, and the filtrate concentrated, leaving 1 - phenyl - 1' - propionylspiro[indoline - 3,4' - piperidine]. In a similar fashion, 1 - phenylspiro[indoline - 3,4' - piperidine] is treated with benzoylchloride to provide 1' - benzoyl - 1 - phenylspiro[indoline - 3,4' - piperidine].

Example 14

A solution of 1 - phenyl - 1' - propionylspiro[indoline - 3,4' - piperidine] (Example 13), in tetrahydrofuran is added dropwise to a stirred suspension of lithium aluminium hydride in tetrahydrofuran. The mixture is heated under reflux for two hours, cooled, quenched cautiously with water and extracted with ether. The ether solution is dried and concentrated to the solid, 1 - phenyl - 1' - n - propylspiro[indoline - 3,4' - piperidine].

Example 15

A solution of 5.0 g of 1' - cyano - 1 - (4 - fluorophenyl)spiro[indoline - 3,4' - piperidine] (Example 6), in 100 ml of tetrahydrofuran is added dropwise to a refluxing mixture of 3 g of lithium aluminium hydride in 100 ml of tetrahydrofuran. After total addition, the reaction mixture is stirred at reflux for three hours and then decomposed with water and dilute sodium hydroxide. The resulting oily product is converted to a crystallized from a methanol-acetone-ether mixture leaving off-white prisms, mp 185—188°C, of 1 - (4 - fluorophenyl)spiro[indoline - 3,4' - piperidine]melate.

Analysis:

Calculated for $C_{18}H_{19}FN_2 \cdot C_4H_4O_4$:	66.32% C;	5.82% H;	7.03% N.
Found:	66.19% C;	5.92% H;	6.96% N.

Example 16

A reaction mixture of 12.4 g of 1' - methylspiro[indoline - 3,4' - piperidine] (Example 1b), and 17.2 g of o-fluoronitrobenzene is maintained at a temperature of from 170—175°C under nitrogen for five hours. The resulting product solidifies at ambient temperature. The solid is pulverized and triturated with 350 ml of an ether-hexane (1:4) mixture, collected by filtration through a course sintered glass funnel and air dried. The dried product is dissolved in chloroform and treated portionwise with 9.7 ml of triethylamine, leaving a slurry. The slurry is poured into water and the organic phase collected and filtered. The filtrate is collected, washed with chloroform and the combined organic solutions are, successively, washed twice with water, dried and concentrated to dryness. The resulting residue is recrystallized from hot isopropyl ether, leaving the pure product, mp 132—132.5°C, of 1 - (2 - nitrophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine].

Analysis:

Calculated for $C_{19}H_{21}N_3O_2$:	70.57% C;	6.54% H;	12.99% N.
Found:	70.80% C;	6.75% H;	12.99% N.

Example 17

A large excess, about 20—25 g, of zinc dust is added potionwise to a vigorously stirring solution, at about 0°C, of 10.7 g of 1 - (2 - nitrophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine] (Example 16), in a combined solvent of 75 ml of ethanol and 5 ml of concentrated hydrochloric acid. After total addition, an additional 15 ml of concentrated hydrochloric acid is carefully added to maintain the temperature of the reaction mixture below 70°C. The reaction mixture is basified with concentrated ammonia, and the alkaline mixture is filtered and concentrated to dryness. The residue is partitioned between 400 ml of methylene dichloride and 400 ml of 10% sodium hydroxide. The organic portion is successively washed three times with 400 ml portions of 10% sodium hydroxide and then once with a 400 ml portion of water, dried and concentrated to dryness, leaving a black glassy product. The product is converted to its hydrochloride in ether which is recrystallized from a methanol-ether mixture to leave the salt, mp 243°C, dec, of 1 - (2 - aminophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine]dihydrochloride.

Analysis:

Calculated for $C_{19}H_{23}N_2 \cdot 2\,HCl$:	62.30% C;	6.89% H;	11.47% N.
Found:	62.40% C;	6.96% H;	11.41% N.

Example 18

Ice water is added to a mixture of 1.8 g of 1' - methylspiro[indoline - 3,4' - piperidine] (Example 1b), 1.5 ml of 2-chlorofluorobenzene, 1.0 g of sodium hydride in 30 ml of dimethyl sulphoxide which was stirred at 50°C under nitrogen for one hour. The biphasic mixture is extracted thrice with ether and the combined ether extracts are shaken with a large excess of 2 N hydrochloric acid. The neutral fraction is discarded and the acidic solution basified, leaving an oil. The oil is dissolved in ether, dried and converted to a crystalline maleate which is recrystallized from an ethanol-ether mixture to give off-white crystals, mp 178.5—179°C of 1 - (2 - chlorophenyl) - 1' - methylspiro[indoline - 3,4' - piperidine]maleate.

Analysis:

Calculated for $C_{19}H_{21}ClN_2 \cdot C_4H_4O_4$:	64.40% C;	5.88% H;	6.53% N;	8.27% Cl.
Found:	64.41% C;	6.00% H;	6.35% N;	8.22% Cl.

Example 19

a). A solution of 4.4 g of 2,5-difluorobenzyl cyanide in 50 ml of dimethyl sulphoxide is carefully added to 2.9 g of 98% sodium hydride. After total addition, the solution is permitted to stand at ambient temperature for 45 minutes before 5.0 g of mechlorethamine hydrochloride in 50 ml of dimethylsulfoxide are added over a 30 minute span. After total addition, the mixture is stirred at 70°C for one hour and allowed to stand at ambient temperature for 16 hours. The mixture is diluted with water and the reaction mixture is extracted three times with ether and the combined ether extracts are shaken with an excess of 2 N hydrochloric acid. The acidic solution is basified with concentrated ammonia, liberating a crude product.

The product is chromatographed through a silica gel column with an eluant of 10% methanol in methylene dichloride. The major fraction, a colourless oil (Rf 0.4) is converted to a crystalline maleate in ether. The salt is recrystallized from an acetone-ether mixture to give colourless crystals, mp 209—211°C, of 4 - cyano - 4 - (2,5 - difluorophenyl) - 1 - methylpiperidine · maleate.

Analysis:
Calculated for $C_{13}H_{14}F_2N_2 \cdot C_4H_4O_4$: 57.95% C; 5.15% H; 7.95% N; 10.79% F.
Found: 58.06% C; 5.14% H; 7.89% N; 10.50% F.

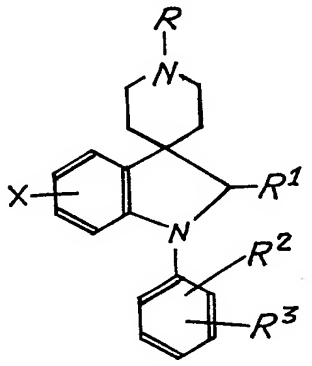
b). A mixture of 2.5 g of 4 - cyano - 4 - (2,5 - difluorophenyl) - 1 - methylpiperidine maleate, 2.4 g of 2 - (3 - chloropropyl) - 2 - (4 - fluorophenyl) - 1,3 - dioxolane, 1.8 g of sodium bicarbonate and 1.8 g of potassium iodide in 25 ml of dimethylformamide is stirred at 80°C for 16 hours. The mixture is allowed to cool, diluted with methylene dichloride and filtered. The filtrate is concentrated under vacuum, leaving a reddish oil which is hydrolysed with a mixture of 25 ml of 3 N hydrochloric acid and 40 ml of ethanol. The mixture is cooled and then basified with 40% sodium hydroxide, liberating an amine. The amine is dissolved in a methylene dichloride ether (1:1) mixture, dried and the solvent is removed under vacuum, leaving a crude product. The product is purified by passing through an alumina column with an ether eluant, to give a pale yellowish oil. The oil is converted to a crystalline maleate in ether, which is recrystallized from a methanol-acetone-ether mixture to give off-white crystals, mp 181—183°C of 1' - [3 - (4 - fluorobenzoyl)propyl] - 1 - (4 - fluorophenyl)spiro[indoline - 3,4' - piperidine]maleate.

Analysis:
Calculated for $C_{28}H_{28}F_2N_2O \cdot C_4H_4O_4$: 68.31% C; 5.73% H; 4.98% N; 6.75% F.
Found: 68.10% C; 5.58% H; 4.64% N; 6.48% F.

WHAT WE CLAIM IS:—

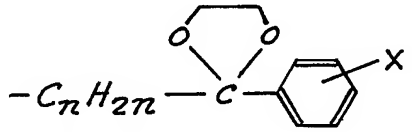
1. A compound of the general formula

(I)



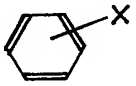
in which

R represents hydrogen or an alkyl, cyano, alkanoyl, phenylalkyl, phenylalkanoyl, alkenyl, cycloalkylalkyl, benzoyl or a benzoylalkyl radical or an ethylene glycol ketal radical of the formula



in which n is an integer of from 1 to 4;

R^1 represents hydrogen or an alkyl radical, a phenyl radical of the formula



or a biphenyl radical;

R^2 and R^3 are the same or different and each represent hydrogen or halogen or a trifluoromethyl, alkyl, alkoxy, hydroxy, nitro, amino or acylamino group; and

X represents hydrogen or halogen or an alkyl, alkoxy, hydroxy or trifluoromethyl group; and

in which in every case the alkyl radical or the alkyl moiety in the alkoxy, alkanoyl and alkenyl radicals is a lower alkyl radical containing up to 4 carbon atoms.

2. A compound as claimed in Claim 1, wherein R represents hydrogen or a lower alkyl, cycloalkylalkyl or benzoylalkyl radical.

3. A compound as claimed in Claim 1 or Claim 2, wherein R^2 represents hydrogen or halogen, or a nitro, amino or trifluoromethyl group; and R^3 and X each represent hydrogen.

4. A compound as claimed in any one of Claims 1 to 3, wherein R represents a methyl group or hydrogen.

5. A compound as claimed in Claim 4, wherein R^2 represents hydrogen or halogen or a trifluoromethyl group; and R^3 and X each represent hydrogen.

6. 1′ - methyl - 1 - (4 - trifluoromethylphenyl)spiro[indoline - 3,4′ - piperidine].

7. 1 - (4 - chlorophenyl) - 1′ - methylspiro[indoline - 3,4′ - piperidine].

8. 1′ - methyl - 1 - phenylspiro[indoline - 3,4′ - piperidine].

9. 1 - (4 - fluorophenyl) - 1′ - methylspiro[indoline - 3,4′ - piperidine].

10. 1 - (2 - chlorophenyl) - 1′ - methylspiro[indoline - 3,4′ - piperidine].

11. 1′ - [3 - (4 - fluorobenzoyl)propyl] - 1 - (4 - fluorophenyl)spiro[indoline - 3,4′ - piperidine].

12. 1 - (4 - fluorophenyl)spiro[indoline - 3,4′ - piperidine].

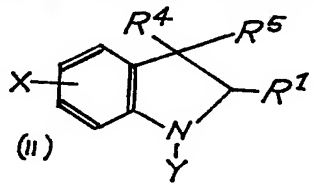
13. 1 - (2 - nitrophenyl) - 1′ - methylspiro[indoline - 3,4′ - piperidine].

14. 1 - (2 - aminophenyl) - 1′ - methylspiro[indoline - 3,4′ - piperidine].

15. Any one of the compounds as claimed in Claim 1 in which is specifically mentioned herein, other than the compounds claimed in Claims 6 to 14.

16. A physiologically tolerable salt of a compound as claimed in any one of Claims 1 to 15.

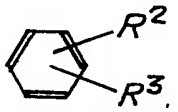
17. A process for preparing a compound of the general formula



(II)

in which

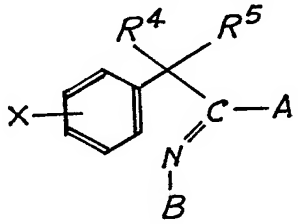
Y represents hydrogen or



R^4 and R^5 each represent an alkyl, aminoalkyl, alkylaminoalkyl or a dialkylaminoalkyl radical,

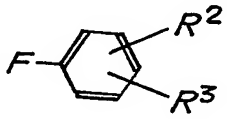
in which in every case the alkyl moiety contains up to 4 carbon atoms, or R^4 and R^5 together with the carbon atom to which they are attached form a cycloalkyl moiety of 3 to 6 carbon atoms in which cycloalkyl a carbon atom may be replaced by >N—R, and

R^1, R^2, R^3, R and X have the meanings as given in Claim 1, which comprises reductively cyclizing a compound of the formula

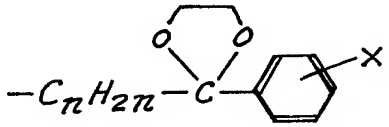


wherein A represents R^1, B represents hydrogen, or A and B together form an additional bond, R^4, R^5, X and R^1 are as defined above to provide a compound of

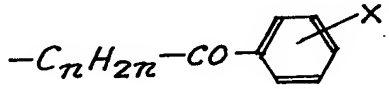
the formula (II) wherein Y represents hydrogen and R^1, R^4, R^5 and X are as defined above, and reacting that compound with a compound of the formula



wherein R^2 and R^3 are as defined above, except that they cannot be hydroxy, amino or acylamino, to provide a compound of formula (II), wherein Y is not hydrogen, and, if desired, treating a compound of the formula (II), wherein R represents methyl, with cyanogen bromide to provide a compound of the general formula (I), wherein R represents cyano, and optionally splitting the cyano group to provide a compound of the formula (I), wherein R represents hydrogen and, if desired, alkylating or acylating that compound to provide a compound of the formula (I), wherein R is as defined above except that it is not hydrogen or cyano, and, if desired, hydrolyzing a compound of the formula (II), wherein R represents



to provide a compound of the formula (II), wherein R represents



and, if desired, reducing a compound of the formula (II), wherein R contains a carbonyl group, to provide a compound of the formula (II), wherein the carbonyl group in R is replaced by a methylene group and, if desired, dealkylating a compound of the formula (II), wherein X, R^2 and/or R^3 each represent an alkoxy group, to provide the corresponding phenolic compound, and, if desired, reducing a compound of the formula (II), wherein R^2 or R^3 represents nitro, to provide the corresponding amino compound and, if desired, acylating a compound of the formula (I), wherein R^2 and/or R^3 represents amino to provide the corresponding acylamino group.

18. A process as claimed in Claim 17, wherein a compound of the general formula (I) given in Claim 1 is prepared.

19. A process as claimed in Claim 17, substantially as described in any one of the Examples herein.

20. A pharmaceutical preparation which comprises a compound as claimed in any one of Claims 1 to 16, in admixture or conjunction with a pharmaceutically suitable carrier.

21. A pharmaceutical preparation as claimed in Claim 20, which is in a dosage form suitable for oral administration.

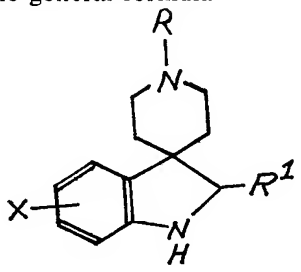
22. A pharmaceutical preparation as claimed in Claim 20, which is in a dosage form suitable for parenteral administration.

23. A pharmaceutical preparation as claimed in Claim 21, which contains in dosage unit form from 1.0 to 300 milligrams of the active ingredient.

24. A pharmaceutical preparation as claimed in Claim 22, which contains in dosage unit form from 0.5 to 100 milligrams of the active ingredient.

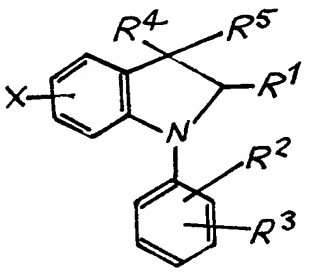
25. A method of treating a non-human mammal which comprises administering a compound as claimed in any one of Claims 1 to 16.

26. A compound of the general formula



in which R, R^1 and X have the meanings given in Claim 1, and a physiologically tolerable salt thereof.

27. A compound of the general formula



in which R^1, R^2, R^3 and X have the meanings given in Claim 1, and R^4 and R^5 have the meanings given in Claim 17 and a physiologically tolerable salt thereof.

ABEL & IMRAY,
Chartered Patent Agents,
Northumberland House,
303—306 High Holborn,
London, WC1V 7LH.

Printed for Her Majesty's Stationery Office, by the Courier Press, Leamington Spa, 1981
Published by The Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.